Commentary

Is clopidogrel superior to aspirin in secondary prevention of vascular disease?

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Received: 15 September 2000
Revisions requested: 9 October 2000
Revisions received: 17 October 2000
Accepted: 10 November 2000
Published: 30 November 2000

Curr Control Trials Cardiovasc Med 2000, **1**:143–145

(Print ISSN 1468-6708; Online 1468-6694)

Abstract

The cornerstone in clinical evidence of the relative efficacy of thienopyridines (clopidogrel, ticlopidine) versus aspirin in the secondary prevention of vascular disease is the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events trial. This trial showed a modest benefit in the reduction of vascular events by clopidogrel. The results differed according to qualifying disorder: myocardial infarction, −3.7%; ischaemic stroke, +7.3%; and peripheral arterial disease, +23.8% ($P = 0.042$). Similar results were found for ticlopidine after brain ischaemia. The safety of clopidogrel appears to be similar to that of aspirin and better than that of ticlopidine. However, the recent report of thrombotic thrombocytopenic purpura in association with clopidogrel causes concern.

Keywords: aspirin, cerebral ischaemia, clopidogrel, myocardial infarction, peripheral artery disease

Introduction

A nice bottle of Graves arrived at our offices in early August 2000. The Dutch branch of Sanofi-Synthelabo sent this wine to collaborators of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial [1] to celebrate the regulation of reimbursement for clopidogrel in the Netherlands on 26 July. The official indication for this novel antiplatelet drug reads: 'secondary prevention in patients with atherosclerotic disease *and* proven aspirin sensitivity'. Sanofi-Synthelabo appealed against the limitation to patients intolerant to aspirin, but lost the lawsuit [2].

CAPRIE: clopidogrel versus aspirin

What is the background of this legal quarrel? The cornerstone is clinical evidence from the CAPRIE trial, a randomised, blinded, international study [1]. Clopidogrel (75 mg daily) and aspirin (325 mg daily) were compared in the prevention of the composite outcome event 'vascular death, nonfatal stroke or nonfatal myocardial infarction'. Clopidogrel reduced the annual risk of such a vascular event from 5.83 to 5.32% in comparison with aspirin, corresponding to a relative risk reduction (RRR) of 8.7%. The 95% confidence interval just kept clear of the neutral value and ranged from 0.3 to 16.5%. The design of the study

CAPRIE = Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events; RRR = relative risk reduction; TIA = transient ischaemic attack.

was based on the paradigm prevalent in the early 1990s: all clinical presentations of atherosclerotic disease should be regarded as different manifestations of a single disorder of the arterial vascular tree. The data of the CAPRIE trial do not necessarily support this paradigm, because the RRR values of the three diagnostic strata (each with over 6000 patients) differed considerably: −3.7% for myocardial infarction, +7.3% for ischaemic stroke, and 23.8% for peripheral arterial disease ($P = 0.042$). A similar difference between different categories of atherosclerotic disease had been observed by the AntiPlatelet Trialists' Collaboration [3]. The RRR values achieved by aspirin (compared with placebo) ranged from 18% for cerebral ischaemia to 35% for unstable angina.

All thienopyridines versus aspirin

Clopidogrel is a thienopyridine chemically related to the already available ticlopidine. Both thienopyridines block the activation of platelets by selective and irreversible inhibition of binding of ADP to its platelet receptor. A recent review by the Cochrane Library reviewed the effects of this class of drugs [4,5]. Four trials on the comparison of thienopyridines with aspirin, with a total of 22,656 patients, were identified. Most information came from the CAPRIE trial (72% of the outcome events) and virtually all other data originated from the Ticlopidine Aspirin Stroke Study [6]. This latter trial enrolled patients with a recent transient ischaemic attack (TIA) or minor ischaemic stroke and found a 6% RRR (95% confidence interval, −7% to +17%) of vascular events [7], an effect quite similar to that observed in the CAPRIE stroke stratum.

Side effects

One of the reasons for developing clopidogrel was the risk of neutropenia with ticlopidine use (neutropenia occurred in 2.3% of the ticlopidine treated patients in the Ticlopidine Aspirin Stroke Study [6]) necessitating monitoring of white blood cell counts. This side effect occurred far less frequently in the CAPRIE trial, which closely monitored for these events; no differences in this regard were observed between clopidogrel and aspirin [1]. With respect to other side effects, more skin rash and diarrhoea were reported with clopidogrel whereas aspirin use led to more upper gastrointestinal discomfort, gastrointestinal haemorrhage and abnormalities of the liver function [1]. The *New England Journal of Medicine* posted an expedited publication on its website earlier this year on 11 cases of thrombotic thrombocytopenic purpura [8], which was triggered by similar adverse effects from ticlopidine. The rate of thrombocytopenic purpura associated with clopidogrel (3.7 per million) appears to be similar to what might be expected in the community [9]. The recent publicity on this life threatening side effect is, however, likely to increase the awareness of clinicians of clopidogrel related thrombocytopenic purpura, which might lead to more such reports.

Which outcome measure?

Another issue is whether the primary outcome of the CAPRIE trial should consist of the composition of several types of vascular events. Albers [10] recently argued that stroke trials should use stroke as an outcome, rather than all vascular events. His main argument was of a statistical nature: because the most important effects in a stroke trial are obtained in the prevention of stroke, the inclusion of non-stroke vascular events would dilute such an effect. Sample size requirements for future trials would thus be less stringent. We disagree with Albers' reasoning on two points. Most important, this approach departs from the patient's perspective. A patient presenting with vascular disease, either cerebrovascular, cardiac, or peripheral, has a high risk of future vascular events anywhere in the arterial tree. Indeed, new events tend to be most frequent in the presenting organ during the first years after presentation, but the whole vascular bed is later at risk. Because a patient does not want to be harmed by either a stroke or a myocardial infarction, protection against any such event should be offered. Trials should thus be designed in such a way that they can address this point of view by means of a composite vascular outcome event. One may even argue, from the patient's perspective, to include major bleeding complications as one of the most important side effects in the evaluation of antithrombotic treatment [11]. A second objection to Albers' reasoning is that sample size requirements need not necessarily be advantageous with a stricter outcome definition. The benefit gained by a (expected) higher treatment effect may be offset by a smaller number of outcome events. We thus consider the choice of the primary outcome event of the CAPRIE trial appropriate for use in clinical practice. Restricted outcome definitions, which always come free with the use of composite events, may nevertheless be useful in unravelling pathophysiological mechanisms.

Costs and the market

Would clopidogrel be cost effective in secondary prevention? Hankey and Warlow calculated that it would cost approximately US$33,000 to avoid one stroke in secondary stroke prevention with clopidogrel, whereas aspirin would cost only US$1400 in the same situation [12]. Meanwhile, Sanofi-Synthelabo and Bristol-Meyers advertise their drug and are sometimes overenthusiastic about clopidogrel. One advertisement stated that clopidogrel reduced the number of ischaemic events by 26% compared with aspirin treatment [13]. This misleading number represented a relative efficacy, on comparison with an imaginary placebo group, derived from data of the AntiPlatelet Trialists' Collaboration.

New research

At least one new study with clopidogrel as a secondary prevention drug is about to start. The combination of 75 mg clopidogrel and 75 mg aspirin daily will be compared with

clopidogrel only in the MATCH trial (ie Management of ATherothrombosis with Clopidogrel in High-risk patients with recent TIA or ischaemic stroke). The primary outcome of this trial will be the same composite event used in the CAPRIE trial extended with rehospitalisation for acute ischaemic events. The study aims to enrol 7600 patients with ischaemic brain disease. The atherosclerosis paradigm has clearly lost its attractiveness in the new millennium. The MATCH study will also not answer the question whether it is useful to add clopidogrel to aspirin, but will answer only the reverse question. More data are available on the efficacy of aspirin, the current standard in patients with ischaemic brain disease, than on the efficacy of clopidogrel [1,14,15].

Conclusions

In summary, clopidogrel appears to be somewhat more effective than aspirin if one is willing to accept the unitary atherosclerosis paradigm. The gain, however, is modest: about 200 patients should use clopidogrel rather than aspirin for 1 year to prevent just one vascular event. If one is sceptical about the atherosclerosis paradigm, there is little reason to use clopidogrel after myocardial infarction and good grounds to replace aspirin by clopidogrel in peripheral arterial disease. The data are not convincing after ischaemic stroke, and cost considerations would tip the balance in favour of aspirin. The conservative attitude of the Dutch authorities in their regulation of reimbursement of clopidogrel is understandable. We have to await the results of studies on the combined efficacy of clopidogrel and aspirin for a reassessment of the position of clopidogrel.

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